UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,832	11/29/2001	Robert Chow	020035-001100US	7166

20350 7590 10/14/2010

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
10/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,832	CHOW ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,20,24,25,28-31,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 20, 24-25, 28-31 and 33-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments and arguments filed August 4, 2010 have been received and entered. Claim 1 has been amended.

Claims 1, 20, 24-25, 28-31 and 33-34 are under consideration.

Withdrawn-Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20, 24-25, 28-31 and 33-34 were rejected under 35 U.S.C.§112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. The previous office action indicated an enabled scope for a method for treating HIV infection in a human in need thereof, wherein HIV entry into an immune cell is facilitated by a CCR5 receptor, said method comprising: (a) screening a plurality of human donors for the presence of a beneficial gene to identify a stem cell-rich population of cells having the beneficial gene; wherein the stem cell-rich population of cells has a beneficial gene has a homozygous polymorphism of a 32 basepair deletion in the coding region of the CCR5 gene and the encoded CCR5 receptor does not facilitate HIV entry into the immune cell, (b) transplanting said stem cell-rich population into the human in need thereof, and wherein the immune cells of said human are reduced or eliminated prior to transplantation, thereby treating said HIV infection, wherein HIV entry into the immune cell of said human is facilitated by the CCR5 receptor and wherein the stem cell-rich population of cells is umbilical cord blood. Applicants' amendments to the base claim limiting the scope of the claims to the enabling embodiments obviates the basis of the rejection. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1, 20, 24-25, 30, and 31 were rejected under 35 U.S.C. 103(a) as being unpatentable over Piccachio et al (J Virol. 1997; 71(9): 7124-7), Contu et al . (Bone Marrow

Transplant 1993, 12: 669–671) , Hariharan (AIDS Res Hum Retroviruses. 1999 Nov 20;15(17):1545-52) and Quillent et al (Lancet. 1998; 351(9095): 14-8). Applicants' cancellation of the limitation "CCR5m303" from claim 1 renders their rejections moot. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 20, 24-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Piccachio et al (J Virol. 1997; 71(9): 7124-7), Contu et al (Bone Marrow Transplant 1993, 12: 669–671) and Hariharan (AIDS Res Hum Retroviruses. 1999 Nov 20; 15(17):1545-52.).

Piccachio et al teach a method of screening plurality of human donors for the presence of a beneficial gene having a homozygous polymorphism of a 32 basepair deletion in the coding region of the CCR5 gene and the encoded CCR5 receptor does not facilitate HIV entry into the immune cell by PCR amplification. Piccachio et al further teaches transplanting cells with different genotypes (homozygous mutant CCR5△32/△32, heterozygous mutant CCR5△32/ + or wild type CCR5+/+) from human donors in a subject (SCID mouse). The subjects were subsequently infected with HIV virus. It is noted that homozygous mutant CCR 5 mice were resistant of infection from M tropic virus (see page 7124, col. 2, table 2 and figure 1) (limitation of claim 1). Piccachio et al further teaches screening for a cell sample from a human donor to identify cells having polymorphism in CCR5 using sequencing meeting the limitation of claims 24-25). Although, Piccachio et al provided proof of principle for a method of transplanting

blood cells comprising stem cell-rich population into a subject that is infected with HIV, thereby treating said HIV infection and wherein the immune cells of said subject are reduced prior to transplantation, but differ from claimed invention by not disclosing screening polymorphism of CCR 5 gene in stem cell population to a human subject.

However, prior to instant invention Contu et al teach identification of HLA genotype of bone marrow cells and reported administering HLA-identical allogeneic bone marrow cell transplant after cytoablation with busulphan and cyclophosphamide to a human subject infected with HIV meeting the limitation of claims 1 and 20. Contu et al reported engraftment of cells upon transplantation and were negative for HIV after 30 days (see abstract). Although, Contu et al teach administering HLA-identical allogeneic bone marrow transplant to a human subject infected with HIV, but differ from claimed invention by not disclosing cell derived from cord blood.

However, such was known in prior art. For instance, Hariharan et al disclose advantage of using human placental cord blood (HPCB) as being a rich source of hematopoietic stem cells having considerably greater proliferative capabilities compared to similar cells from bone marrow (page 1546, column 1, lines 3-5). It is noted that Hariharan emphasized on studying HIV-1 co-receptor expression in placental cord blood-isolated stem cells and their susceptibility to HIV-1 infection, because Hariharan noted that this unique subset of stem cells could be preferentially used in transplant situations (page 1546, column 3, paragraph 1 and Figure 1).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Piccachio and Contu by screening of donors for identifying population of stem cells having CCR5 mutation that are derived from cord blood, as Hariharan had already described the therapeutic use of cord derived stem cells in cell transplant. In addition, Piccachio provided motivation by suggesting that subject with homozygous deletion of delta 32 CCR5 are protected to some extent from HIV infection. One of ordinary skill in the art would have been motivated to identify a population of stem cell population from a donor having a homozygous mutant CCR5 △32/ △32 genotype for cell transplant as suggested by Hariharan in the method of Contu for the treatment of HIV. One who would practice the invention would have had reasonable expectation of success because Piccachio had already described a method to identify and screen beneficial polymorphism in a CCR5 gene in a human donor and transplanting said cell in a subject to reduce HIV infection. It would have only required routine experimentation to screen and identify beneficial polymorphism in a CCR5 gene that is 32 bp homozygous deletion in the coding region of CCR5 gene of cord blood derived stem cell from human donor for the transplantation in human subject . One of ordinary skill in art would have been motivated to combine the teaching of Piccachio, Contu et al and Hariharan because method for screening stem cells population derived from cord blood having CCR5 delta 32 mutation would have allowed skilled artisan to study the usefulness of these cells in gene and cell therapy. Applicants should note that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S.-, 82USPQ2d 1385 (2007). Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1, 24, 28-31 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piccachio et al (J Virol. 1997; 71(9): 7124-7), Contu et al . (Bone Marrow Transplant 1993, 12: 669–671) and Hariharan (AIDS Res Hum Retroviruses. 1999 Nov 20;15(17):1545-52.) as applied to claims 1, 20, 24-25, above, and further in view of Kaneshige et al (MHC & IRS, Supplement Vol. 1, 1994, 159-164).

The combined teachings of Piccachio et al, Contu et al and Hariharan have been discussed above and are relied upon in same manner. The combination of reference teach a method of treating HIV infection in a subject in need thereof by transplanting a population of cord blood cells having a beneficial polymorphism in CCR5 gene, but differ from claimed invention by not identifying the HLA genotype or phenotype of said cell.

The deficiency is cured by Kaneshige et al who reported a method for identifying an HLA genotype of a subject by (a) obtaining a sample comprising a template nucleic acid from said subject (b) amplifying said template nucleic acid with a plurality of HLA allele specific forward and reverse primers to get amplification products (c) then hybridizing said amplification product with HLA locus specific capture oligonucleotide immunobilized in a solid phase to form a plurality of detectable complexes and detecting said detectable complex to identify said HLA genotype of said subject (see page 159-160) meeting the limitation of claims 24-31. It is also noted that in the method of Kaneshige, the template nucleic acid is genomic DNA isolated from blood samples (see page 159), the HLA genotype is class II genotype and the detectable label is the binding protein biotin.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Piccachio, Contu et al and Hariharan by performing HLA genotyping of cells using methods disclosed by Kaneshige. One of ordinary skill in the art would have been motivated to identify HLA genotype of stem cell population from donors having a beneficial polymorphism in CCR5 gene by determining the HLA genotype of the sample for the purposes of stem cell banking. The limitation of claims 33-34 would have been obvious in view of teaching of Contu et al and Piccachio who reported multiple administrations of different blood derived stem cells with the beneficial gene reduced HIV viral load. One who would practice the invention would have had reasonable expectation of success because Piccachio, Contu et al, Hariharan had already described a method to identify and screen beneficial polymorphism in CCR5 gene. It would have only required routine experimentation identify the HLA genotype in this population of stem cells for using HLA matched or unmatched genotype in cell transplant and cell banking purposes as taught by Kaneshige. One of ordinary skill in art would have been motivated to combine the teaching of Piccachio, Contu, Hariharan and Kaneshige because a method identifying HLA genotype of population derived from cord blood having beneficial polymorphism in CCR5 gene would have allowed skilled artisan to use these cells in cell therapy.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1, 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rader et al (US 20030039642 A1, dated 02/27/2003, effective filing date 7/18/2001), Balotta (AIDS. 1997, 11(10): F67-71) and Hariharan (AIDS Res Hum Retroviruses. 1999 Nov 20; 15(17):1545-52.).

Rader et al teach a method for treating a patient infected with HIV, the method comprising the steps of: administering CCR5-def hematopoietic stem cells to the patient via intravenous injection; and administering CCR5-def neuronal stem cells to the patient via subcutaneous injection, wherein administration of the hematopoietic and neuronal stem cells is preceded by aplasia of the patient's marrow (see claim 1 and 2 of '642). Although, Rader et al teach a method of transplanting blood cells comprising stem cell-rich population into a subject that is infected with HIV, thereby treating said HIV infection and wherein the immune cells of said subject are reduced prior to transplantation, but differ from claimed invention by not disclosing screening polymorphism of CCR 5 gene being 32 bp deletion in coding region of CCR5 gene.

Balotta et al teach a method of screening polymorphism of CCR-5 gene in a subjects, said method comprising (a) collection of blood samples from 122 blood donors, (b) and subsequent analysis of CCR-5 gene polymorphism have 32 bp deletion in coding region of CCR5 by RT-PCR (see page F68, column 1, last paragraph, bridging to column 2, paragraph 1-3). Balotta et al also conclude partial protection from HIV-1 infection in subjects having delta32 homozygous deletion in the CCR-5 gene (see page F71, last paragraph). However, Balotta et al do not teach screening polymorphism of CCR 5 gene in stem cell population derived from cord blood.

However, such was known in prior art. For instance, Hariharan et al disclose advantage of using human placental cord blood (HPCB) as being a rich source of hematopoietic stem cells having considerably greater proliferative capabilities compared to similar cells from bone marrow (page 1546, column 1, lines 3-5). It is noted that Hariharan emphasized on studying HIV-1 co-receptor expression in placental cord blood-isolated stem cells and their susceptibility to HIV-1 infection, because Hariharan noted that this unique subset of stem cells could be preferentially used in transplant situations (page 1546, column 3, paragraph 1 and Figure 1).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Rader by screening of donors for identifying population of stem cells having CCR5 mutation that are derived from cord blood, as Hariharan had already described the therapeutic use of cord derived stem cells in cell transplant. In addition, Balotta et al provided motivation by suggesting that subject with homozygous deletion of delta 32 CCR5 are protected to some extent from HIV infection. One of ordinary skill in the art would have been motivated to identify a population of stem cell population from a donor having a homozygous mutant CCR5 △32/ △32 genotype for cell transplant as suggested by Hariharan. One who would practice the invention would have had reasonable expectation of success because Rader and Ballota had already described a method to identify and screen beneficial polymorphism in a CCR5 gene in a human donor and transplanting said cell in a subject to reduce HIV infection. It would have only required routine experimentation to screen and identify beneficial polymorphism in a CCR5 gene that is 32 bp homozygous deletion in the coding region of CCR5 gene of cord blood derived stem cell from human donor for the transplantation in human

subject. One of ordinary skill in art would have been motivated to combine the teaching of Rader, Balotta et al and Hariharan because method for screening stem cells population derived from cord blood having CCR5 delta 32 mutation would have allowed skilled artisan to study the usefulness of these cells in cell therapy.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 20, 28-31 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rader et al (US 20030039642 A1, dated 02/27/2003, effective filing date 7/18/2001), Balotta (AIDS. 1997, 11(10): F67-71) and Hariharan (AIDS Res Hum Retroviruses. 1999 Nov 20; 15(17):1545-52.) as applied to claims 1, 24-25 above, and further in view of Kaneshige et al (MHC & IRS, Supplement Vol. 1, 1994, 159-164) or Contu et al (Bone Marrow Transplant 1993, 12: 669–671).

The combined teachings of Rader, Balotta and Hariharan have been discussed above and are relied upon in same manner. The combination of reference teach a method of treating HIV infection in a subject in need thereof by transplanting a population of cord blood cells having a beneficial polymorphism in CCR5 gene, but differ from claimed invention by not identifying the HLA genotype or phenotype of said cell.

The deficiency is cured by Kaneshige et al who reported a method for identifying an HLA genotype of a subject by (a) obtaining a sample comprising a template nucleic acid from said subject (b) amplifying said template nucleic acid with a plurality of HLA allele specific forward and reverse primers to get amplification products (c) then hybridizing said amplification product with HLA locus specific capture oligonucleotide immunobilized in a solid phase to form a plurality of detectable complexes and detecting said detectable complex to identify said HLA genotype of said subject (see page 159-160). It is also noted that in the method of Kaneshige, the template nucleic acid is genomic DNA isolated from blood samples (see page 159), the HLA genotype is class II genotype and the detectable label is the binding protein biotin. Contu et al teach identification of HLA genotype of bone marrow cells and reported administering HLA-identical allogeneic bone marrow transplant after cytoablation with busulphan and cyclophosphamide to a human subject infected with HIV. Contu et al reported engraftment of cells upon transplantation and were negative for HIV after 30 days (see abstract). Although, Contu et al teach administering HLA-identical allogeneic bone marrow transplant to a human subject infected with HIV, but differ from claimed invention by not disclosing stem cell derived from cord blood.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Rader, Balotta and Hariharan by performing HLA genotyping of cells using methods disclosed by Kaneshige/ Contu. One of ordinary skill in the art would have been motivated to identify HLA genotype of stem cell population from donors having a beneficial polymorphism in CCR5 gene by determining the HLA genotype of the sample for the purposes of stem cell banking. The limitation of claims 33-34 would have been obvious in view of teaching of Contu et al and Rader who reported multiple administrations of different blood

derived stem cells with the beneficial gene for reducing HIV load. One who would practice the invention would have had reasonable expectation of success because Rader, Balotta, and Hariharan had already described a method to identify and screen beneficial polymorphism in CCR5 gene. It would have only required routine experimentation identify the HLA genotype in this population of stem cells for using HLA matched or unmatched genotype in cell transplant and cell banking purposes as taught by Kaneshige/ Contu. One of ordinary skill in art would have been motivated to combine the teaching of Rader, Balotta and Hariharan with , Contu/ Kaneshige because a method identifying HLA genotype of population derived from cord blood having beneficial polymorphism in CCR5 gene would have allowed skilled artisan to use these cells in clinical cell therapy.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to arguments

Piccachio et al, Contu and Hariharan

Applicants disagree with the rejection of claim 1 over Piccachio et al, Contu and Hariharan, arguing that Piccachio do not teach a method of treating HIV infection in a human infected with HIV infection (page 6, last para and page 7, first para.). Applicants further argue that Contu et al do not teach claimed method and method also involve anti HIV therapy and does not involve cell that has been screened for a beneficial gene having homozygous deletion of CCR5 gene (see page 7, last, para.). Applicants further argue that Hariharan do not provide teaching missing from the primary reference. Applicant cites various portion of the Hariharan to assert that although highly purified CD34+AC133+ cord blood stem cells showed transcript for CCR5, but CCR protein is not expressed in freshly isolated cells (see page 8). As an initial matter, it is noted that the rejection to claims 30-31 was inadvertently included in the rejection. Therefore, rejection of claims 30-31 are hereby withdrawn. To the extent that Applicants' arguments are pertinent to the standing rejection of claim 1, 20, 24-25, they are addressed as follows: Applicants' arguments have been fully considered, but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of Piccachio et al. to formulate the grounds for not teaching

the invention. It should be noted that the ultimate goal of transplanting human peripheral blood mononuclear cell comprising stem cells having 32bp homozygous deletion in CCR5 is to study the impact of CCR5△32/△32 in HIV infected subject. In this regard, as previously indicated, Piccachio et al in describing the method teach screening plurality of human donors for the presence of a beneficial gene having a homozygous polymorphism of a 32 basepair deletion in the coding region of the CCR5 gene and the encoded CCR5 receptor does not facilitate HIV entry into the immune cell by PCR amplification. The cells with different genotypes (homozygous mutant CCR5△32/△32, heterozygous mutant CCR5△32/ + or wild type CCR5+/+) from human donors were transplanted in a subject (SCID mouse). The subjects were subsequently infected with HIV virus. It is noted that homozygous mutant CCR 5 mice were resistant of infection from M tropic virus (see page 7124, col. 2, table 2 and figure 1) (limitation of claim 1). Thus, Piccachio et al provided proof of principle for a method of transplanting blood cells comprising stem cell-rich population into a subject that is infected with HIV, thereby treating said HIV infection and wherein the immune cells of said subject are reduced prior to transplantation. With respect to applicants' argument that Piccachio et al do not teach treating HIV infection in human, it should be noted that if Piccachio had disclosed this limitation, it would have been an anticipation rejection and not an obviousness type rejection. The deficiency of Piccachio et al is cured by Contu who reported the identification of HLA genotype of allogeneic bone marrow cells and reported administering HLA-identical allogeneic bone marrow cell transplant to a human subject infected with HIV after cytoablation with busulphan and cyclophosphamide. To the extent that Contu et al. describe transplanting HLA-identical human bone marrow cell to a HIV infected human, the rejection is applicable to the instant case. Applicants' selective reading of Piccachio et al ignores the teachings of the Contu. There is no requirement for Piccachio et al. to teach that which is clearly taught by Contu et al.

In response to applicant's argument that the reference of Contu et al show death of human patient after 10 month of cell transplant, it is noted that the features upon which applicant relies (i.e.,survival beyond 10 month) are not recited in the rejected claims. Furthermore, contrary to applicants' arguments, addition of other retroviral drug prior to or along with cell transplant is not excluded by language set forth in base claims, which is directed to a method comprising administering of a cell population.

In response to applicant's argument that the references of Hariharan et al show mRNA expression of CCR5 but does not express CCR5 protein in freshly prepared CD34+AC133+Cord blood cells, it is noted that the claims are not limited to freshly prepared cord blood or any specific stem cell derived from cord blood as argued by the applicants. Contrary to applicants' assertions, Hariharan et al reported freshly prepared CD34+ cord blood cell as well as CD34+ cell cultured for 7 days (see figure 2) showing transcript for CCR5. Furthermore, Hariharan cite Ruiz et al who reported cultured CD34+ showing surface expression of CCR5 receptor (see page 1551, col. 1, para. 1). To the extent, Hariharan et al disclose the advantage of using human placental cord blood (HPCB) as being a rich source of hematopoietic stem cells having considerably greater proliferative capabilities compared to similar cells from bone marrow (page 1546, column 1, lines 3-5), the rejection is applicable to the instant case. A person of skill in the art at the time of the invention would be motivated to modify the method of Piccachio and Contu by screening of donors for identifying population of stem cells having homozygous CCR5 mutation in the coding region that are derived from stem cells of different origin including cord blood and adminster said cells to a subject having HIV infection in the method of treating HIV infection in human as disclosed by Contu. One of ordinary skill in the art would be motivated to screen for 32bp homozygous deletion in the coding region of CCR5 as the art teaches that subject with such deletion of delta 32 CCR5 are protected from HIV infection (supra), while Hariharan provided motivation to use cord derived stem cells in cell transplant as compared to bone marrow derived cells (page 1546, column 1, lines 3-5). It would have only required routine experimentation to screen and identify beneficial polymorphism in a CCR5 gene that is 32 bp homozygous deletion in the coding region of CCR5 gene from cord, bone marrow or peripheral blood derived stem cell from human donor for the transplantation in human subject. This is because method for screening stem cells population having CCR5 delta 32 mutations and isolation of stem cells from various source including cord, peripheral and bone marrow is routine and known to one of ordinary skill in the art.

Therefore, in view of the fact patterns of the instant case, and the ground of rejection outlined by the examiner, applicants' arguments are not compelling and do not overcome the rejection of record.

In section C on pages 9-10 of the applicants' argument, Applicant re-iterates rely on their previous arguments that have been discussed in preceding section. The arguments are substantially the same as those addressed in the foregoing response.

In section D on pages 10 of the applicants' argument, Applicants argue that Rader *et al.* disclose a method for treating a patient infected with HIV, the method comprising the steps of: administering CCR5-def hematopoietic stem cells to the patient via intravenous injection and administering CCRS-def neuronal stem cells to the patient via subcutaneous injection. However, Rader *et al. differ* "from the claimed invention by not disclosing screening polymorphism of CCR5 gene being 32 bp deletions in the coding region of the CCR5 gene". Applicants further assert that secondary reference teach screening of polymorphism of CCR5 gene being 32 bp deletion in coding region in human peripheral blood cells but do not teach the same in cord blood cells. Applicants further argue that although Hariharan teaches highly purified CD34+AC133+ cord blood stem cells show transcript for CCR5, CCR protein is not expressed in freshly isolated cells (see pages 10-11). Applicant conclude that combination of references do not teach presently claimed method.

As an initial matter, Applicant should note that claims have been re rejected using the reference of Rader *et al.* to demonstrate the use of stem cells derived from different source were routinely used in the treatment of HIV infection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have again engaged in selective reading of the teachings of Rader *et al.* to formulate the grounds for not teaching the invention. It should be noted that Rader *et al* clearly teach isolation of CCR5 homozygous deficient cells from human (see page 4, col. 1, line 1-2). In this regard, Rader *et al.* further disclose that individual carrying homozygous CCR5 deficient mutation are resistant to the initial HIV infection (see page 3, col. 2, para. 39). In view of foregoing it is apparent that, ultimate goal of transplanting human stem cells having homozygous deletion in CCR5 to treat HIV infection in human subject. In this regard, as previously indicated, Rader et al teach a method for treating a patient infected with HIV, the method comprising the steps of: administering via intravenous

injection homozygous CCR5 CCR5-def hematopoietic stem cells to the patient, wherein administration of the hematopoietic is preceded by aplasia of the patient's marrow (see claim 1 and 2 of '642) meeting the limitation of claim 1.

With respect to applicants' argument that Rader et al do not teach screening of polymorphism of CCR 5 gene being 32 bp deletion in coding region of CCR5 gene (see page 10 of the argument), it should be noted that such is taught by Balotta (AIDS. 1997, 11(10): F67-71). To the extent, Balotta describe a method of screening a cell having 32 bp deletion in the coding region of the CCR5 gene in cells derived form donor subject, the rejection is applicable to the instant case. Applicants' selective reading of Rader et al. ignores the teachings of the Balotta. There is no requirement for Rader et al. to teach that which is clearly taught by Balotta and Hariharan et al.

In response to applicants' argument that Hariharan teaches highly purified CD34+ AC133 + cord blood stem cells that do not express CCR5 protein in freshly isolated cells, it should be noted that claims are not limited to freshly prepared cord blood or any specific stem cell derived from cord blood as argued by the applicants. In fact, applicants' own specification teaches "[c]ells screened in this invention are obtained from embryos, marrow, peripheral blood, placental blood, umbilical cord blood, adipose tissue, or any other potential source of stem cells (see specification para. 17)". In view of teaching of the specification, it is clear that to the extent prior art as described above teaches screening of individual having homozygous mutation in the coding region of CCR5 gene; it would have been obvious for one of ordinary skill in the art to transplant any source of stem cells from that individual. In the instant context, Hariharan et al also reported culturing CD34+ cell for 7 days (see figure 2) showing transcript for CCR5. Furthermore, Hariharan cite Ruiz et al who reported cultured CD34+ show surface expression of CCR5 receptor (see page 1551, col. 1, para. 1). To the extent, Hariharan et al disclose the advantage of using human placental cord blood (HPCB) as being a rich source of hematopoietic stem cells having considerably greater proliferative capabilities compared to similar cells from bone marrow (page 1546, column 1, lines 3-5), the rejection is applicable to the instant case. A person of ordinary skill in the art would have been motivated to modify the method of Rader by screening of donors for identifying population of stem cells having 32bp homozygous CCR5 mutation as per the teaching of Balotta in the stem cells derived from cord blood. Hariharan had

already described the therapeutic use of cord derived stem cells in cell transplant. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

In section E on pages 11-12 of the applicants' argument, Applicant re-iterates and relies on their previous arguments that have been discussed in preceding section. The arguments are substantially the same as those addressed in the foregoing response.

Conclusion

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632